Wyeth

Wyeth Pharmaceuticals

Date: December 22, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004D-0378: September 13, 2004 (69 FR 55164-55165)

Dear Sir/Madam:

Wyeth Pharmaceuticals is submitting the following comments on the ICH draft (step 2) guideline entitled *ICH S7B: Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals* (June 10, 2004).

Wyeth is one of the world's largest research-based pharmaceutical and health care companies. It is a leader in the discovery, development, manufacturing, and marketing of prescription drugs and over-the-counter medications, with leading products in women's health care, cardiovascular, central nervous system, anti-inflammatory, infectious disease, hemophilia, and oncology categories, and is also a major manufacturer of preventative vaccines. As such, Wyeth is committed to the development of innovative medicines that will treat unmet medical needs and maximize benefits for patients while minimizing risk.

Wyeth appreciates the opportunity to comment on the above-mentioned ICH draft guideline, and trusts that the Agency will take these comments into consideration when preparing the final guidance document.

The following comments are given for consideration in preparing the final guidance.

- Reference is made to Section 2.4, lines 162 to 164 -- *Results from nonclinical S7B studies...generally do not need to be available prior to first administration in humans.*

  Section 2.4 of the draft guideline appears in conflict with Sections 1.3, 1.4 and 2.3.6. The later three sections imply that the recommended nonclinical studies should be performed prior to the initiation of studies in humans. More specifically, section 1.3 indicates that S7B *extends and compliments* the S7A guideline; section 1.4 indicates *that the principles and recommendations for*

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S7A also apply to S7B; and section 2.3.6 indicates *that the data from the S7B studies should be included in the investigator brochure.*

Moreover, Section 2.4 is also in conflict with ICH M3 and ICH S7A (Section 2.10.1). These guidelines indicate that Safety Pharmacology studies, including those described in the S7B, should be reported prior to first in man (FIM).

We therefore recommend that the draft guidance be revised to clarify whether S7B studies should be conducted prior to the initiation of studies in humans and included in the initial IND submission.

- As previously mentioned, Sections 1.3 and 1.4 of the draft S7B guideline indicate that S7B *extends and compliments* the S7A guideline, and *that the principles and recommendations for S7A also apply to the S7B.* In addition, Section 2.11 of the S7A guideline indicates that studies should be conducted in accordance with GLP.

  The current draft S7B guideline is not clear as to the GLP status of the studies to be conducted under this guideline. We therefore request that the Agency clarify if S7B studies need to be conducted in accordance with the GLP regulations.

- The draft S7B guideline uses the term *safety margins* in Sections 2.2 and 2.3.6. (See Lines 88 and 153).

  The term implies a level of safety that may not be assured from the preclinical data it is based on. We therefore suggest changing the term *safety margin* to *therapeutic index, exposure ratio*, or another appropriate term.

- Lastly, we suggest including clarification on the following topic that is not clearly addressed in the current draft guideline: *Is analysis for concentrations of test article in the physiologic salt solution used in the in vitro studies required?*

We are submitting the enclosed comments in duplicate. Wyeth appreciates the opportunity to comment on the above-mentioned draft guideline, and trusts that the Agency will take these comments into consideration.

Sincerely,

Roy J Baranello Jr

Roy J. Baranello, Jr.
Assistant Vice President,
Worldwide Regulatory Affairs